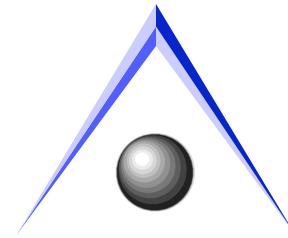


CLUSTER-BASED APPROACHES TO SOLVATION

Mark S. Gordon
Iowa State University
Ames Laboratory



OUTLINE

- Solvation Methods
 - Explicit vs. implicit methods
- Explicit Methods
 - TIP3P, TIP4P
 - SPC, SPC/E
- EFP Method for Solvation
 - Summary of EFP1 method for water
 - Sample input files
 - Monte Carlo method
 - Example applications
- Generalized EFP Method (EFP2)

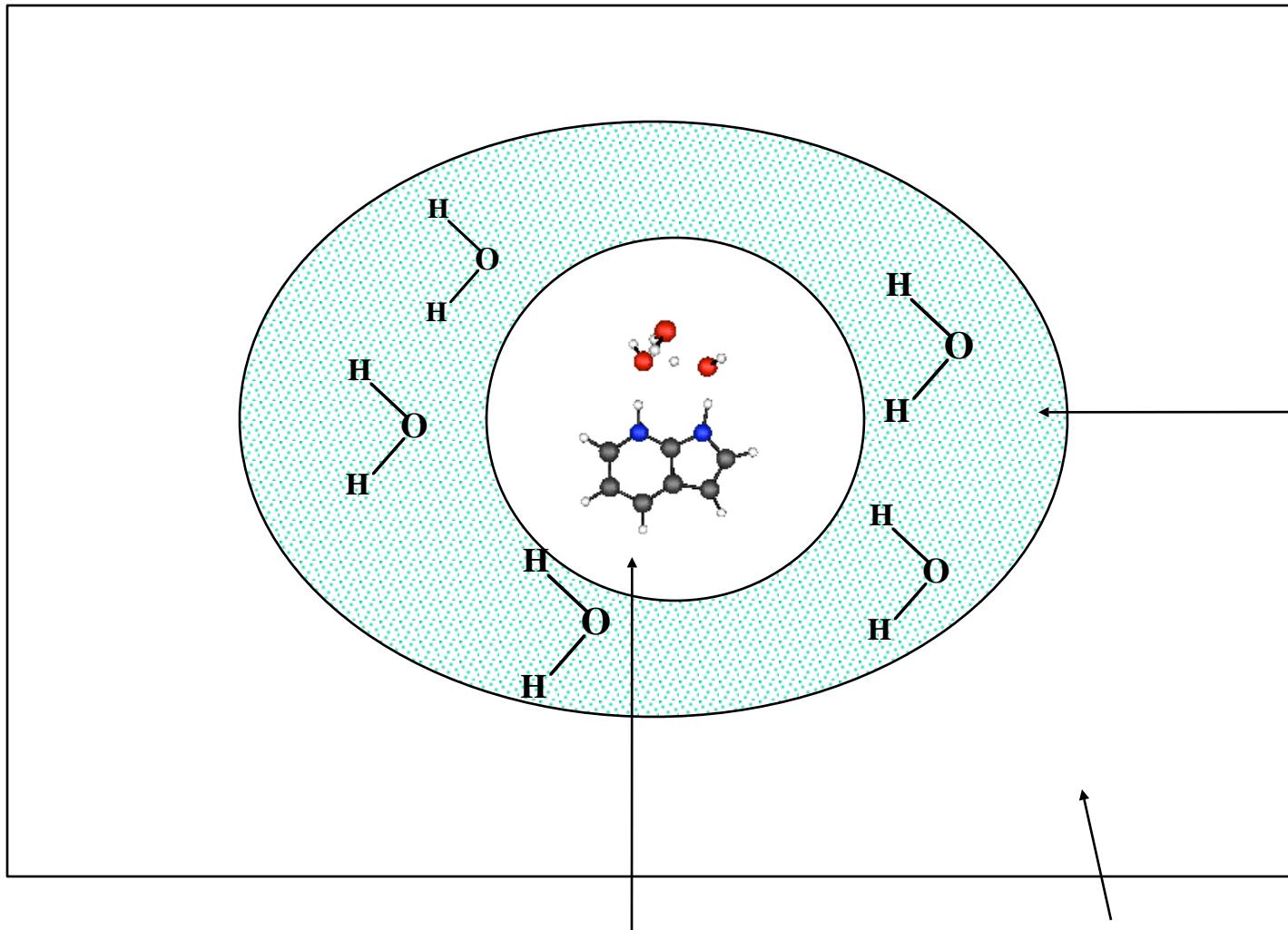
SOLVATION MODELS: CONTINUUM

- Based on Onsager reaction field model
- Computationally efficient
- Sensitive to cavity size and shape
- Do not account for explicit solute-solvent interactions

SOLVATION MODELS: DISCRETE

- Solvent molecules described using potentials
 - Empirical potentials: lots of fitted parameters
 - *Ab initio* potentials: computationally expensive
- Include explicit solute-solvent interactions
- Configurational sampling necessary: computationally demanding

Multi-Layered Approach to Solvation



Ab Initio Solute

Continuum 5

DISCRETE/EXPLICIT MODELS

- TIP3P, TIP4P
 - Jorgensen *etal*, JCP, 79, 926 (1983)
 - Basically simple Lennard-Jones model

$$\varepsilon_{mn} = \sum_i^m \sum_j^n [q_i q_j / r_{ij}] + A / R^{12} - C / R^6$$

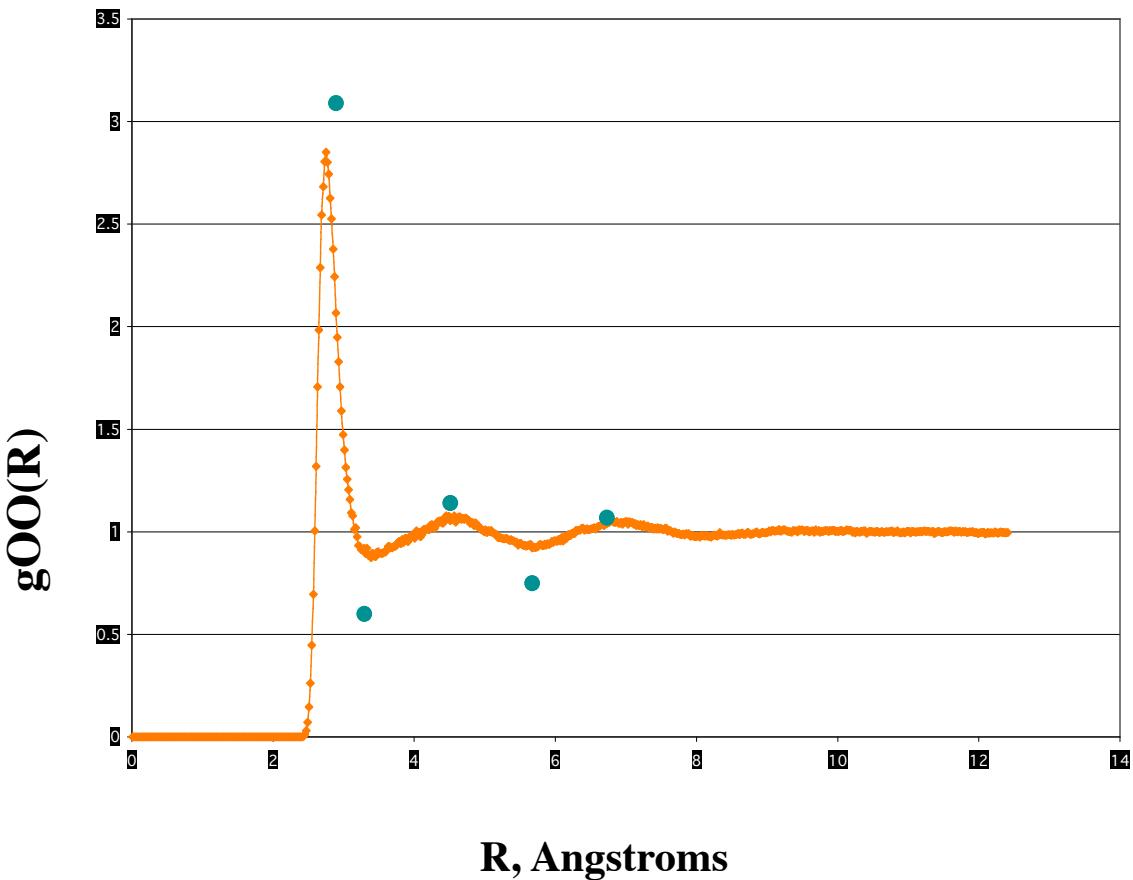
- ε_{mn} =interaction energy between waters m,n
- $q_O < 0 = -2q_H$, A, C fitted to bulk properties
- Rigid molecules
- TIP4P adds a 4th center inside O toward Hs
- Very popular model; doesn't get OO radial distribution function right: misses 2nd peak

DISCRETE/EXPLICIT MODELS

- SPC (Simple Point Charge), SPC/E
 - Berendsen *etal*, JPC, 91, 6269 (1987)
 - SPC:

$$\varepsilon_{mn} = \sum_i^m \sum_j^n [q_i q_j / r_{ij}] + A / R^{12} - C / R^6$$

- SPC same as TIP, but fitted to MD simulations of density and vaporization energy
- Rigid molecules
- Gets OO radial distribution function right
- SPC/E adds polarizability/induction term



Curve: SPC/E
Points: exptl

General Effective Fragment Potential

§ **Discrete** solvation method

§ Fragment potential is one electron contribution
to the *ab initio* Hamiltonian

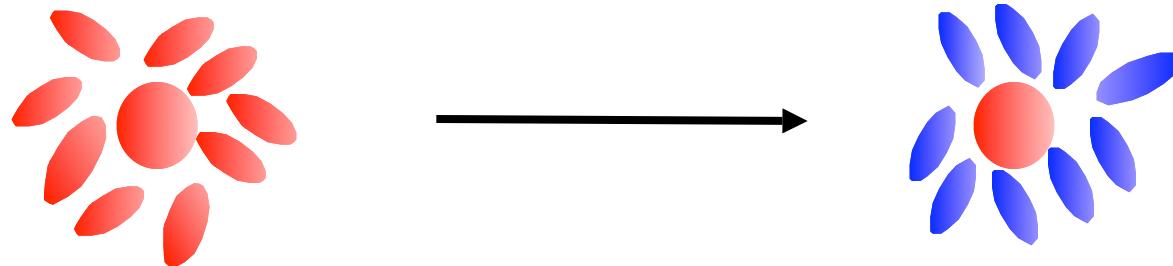
§ Potentials

 are obtained by separate *ab initio* calculations
 depend on properties of **isolated** molecules
 can be systematically improved

Effective Fragment Potential

System is divided into
an *ab initio* region for the “solute” and
a fragment region for the solvent molecules.

$$E = E_{ab\ initio} + E_{\text{interaction}}$$



General EFP Method

In the most general implementation EFP should include all relevant energy contributions:

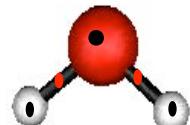
$$E_{\text{interaction}} = E_{\text{Coulomb}} + E_{\text{polarization}} + E_{\text{exch. rep. / charge transfer}} + E_{\text{dispersion}} + E_{\text{higher order terms}}$$

Hartree Fock based EFP

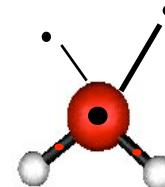
Interaction energy consists of : *electrostatic, polarization and exchange repulsion/charge transfer term*

$$E_{\text{interaction}} = E_{\text{coulomb}} + E_{\text{polarization}} + E_{\text{exchange repulsion/charge transfer}}$$

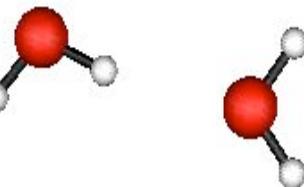
$$E_{\text{interaction}} = \sum_{k=1}^K V_k^{\text{Elec}}(\mu, s) + \sum_{l=1}^L V_l^{\text{Pol}}(\mu, s) + \sum_{m=1}^M V_m^{\text{Re } p}(\mu, s)$$



Distributed
Multipolar expansion



LMO polarizability
expansion



Fit to Functional
Form

Coulomb/Electrostatic Term

$$V_k^{Elec}(\mu, s) = \frac{q_k(\mu)q_s}{r_{sk}} - \sum_a^{\text{x,y,z}} \mu_a^k(\mu) F_a(\mathbf{r}_{sk}) - \frac{1}{3} \sum_{a,b}^{\text{x,y,z}} \Theta_{ab}^k(\mu) F_{ab}(\mathbf{r}_{sk}) - \frac{1}{15} \sum_{a,b,c}^{\text{x,y,z}} \Omega_{abc}^k(\mu) F_{abc}(\mathbf{r}_{sk})$$

where q , μ , Θ and Ω are the charge, dipole, quadrupole and octopole, respectively

F_a , F_{ab} and F_{abc} are the solute electric field, field gradient and field hessian

This DMA is a classical point multipole approach: what if fragments approach each other or solute too closely?:

Classical treatment is then too repulsive: multiply entire expression by damping term to account for overlapping charge densities

$$V_k^{Elec}(\mu, s) \rightarrow (1 - \beta_k(\mu) e^{-\alpha_k(\mu) r_{sk}^2}) V_k^{Elec}(\mu, s)$$

All calculations done once for a given solvent molecule; e.g., water

Polarization/Induction Term

$$V_l^{Pol}(\mu) = - \sum_{a,b}^{x,y,z} F_a(\mathbf{r}_l) \alpha_{ab}^l(\mu) \langle F_b(\mathbf{r}_l) \rangle$$

$$\alpha_{xy}^l = \lim_{F_y \rightarrow 0} \frac{\mu_x^l(F_y) - \mu_x^l(0)}{F_y}$$

Polarizability is treated as a distributed tensor with each tensor located at the centroid of a localized orbital

For water, there are five such LMOs, two O-H bond orbitals, two lone pairs, one inner shell.

F is the field due to the *ab initio* part of the system

α_{xy}^l is a component of the polarizability of the fragment molecule in the lth localized orbital

Iterated to self-consistency

All calculations done once for a given solvent molecule; e.g., water

Exchange Repulsion/Charge Transfer Terms

Fragment-*ab initio* interaction:

$$V_m^{\text{Re } p}(\mu, s) = \sum_j^J \beta_{m,j}(\mu) e^{-\alpha_{m,j}(\mu) r_{m,s}^2}$$

Gaussian functions centered at atom centers and center of mass: J=2, M=4 for water.

Fitted to a set of dimer calculations: several values of R(O-O) for each orientation. Total of 192 points on dimer surface. Fitted to minimize:

$$\Delta = \sum_p^P w_p \left[\left\langle \Psi \left| \sum_m^M V_m^{\text{Re } p} \right| \Psi \right\rangle_p - E_{rem}^{(ab)}(p) \right]^2$$

ω_p is a weighting factor, usually = 1.0; Ψ = *ab initio* wavefunction

Exchange Repulsion/Charge Transfer Terms

Fragment-fragment interaction: similar, except a single exponential function is fitted to the 192 points.

Analytic gradients (first derivatives) have been derived and coded for all terms. So, one can perform geometry optimizations, transition state searches, dynamics

HIGHER-LEVELS OF EFP

- DFT-based EFP (Ivana Adamovic)
 - Same general approach
 - Based on B3LYP
 - Adds some level of correlation
- MP2-based EFP (Jie Song)
 - Same general approach
 - Separate fit for exchange repulsion, remainder
 - More effective correlation, especially at long range

Water hexamer isomers

Binding Energy	DFT B3LYP	MP2	CCSD (T)	HF
prism	62.37	58.25	55.10	42.86
cage	61.84	57.52	54.30	42.49
book	61.34	56.49	53.10	42.44
cyclic	60.57	55.75	52.20	43.10
boat	59.13	54.29	50.80	42.12

- basis set: DH(d,p)

-units: kcal/mol

Water hexamer isomers

Binding Energy	DFT B3LYP	EFP1/ DFT	MP2	CCSD (T)	HF	EFP1/ HF
prism	62.37	61.08	58.25	55.10	42.86	42.42
cage	61.84	61.53	57.52	54.30	42.49	41.90
book	61.34	61.79	56.49	53.10	42.44	41.45
cyclic	60.57	60.65	55.75	52.20	43.10	41.14
boat	59.13	59.37	54.29	50.80	42.12	40.09

- basis set: DH(d,p)

-units: kcal/mol

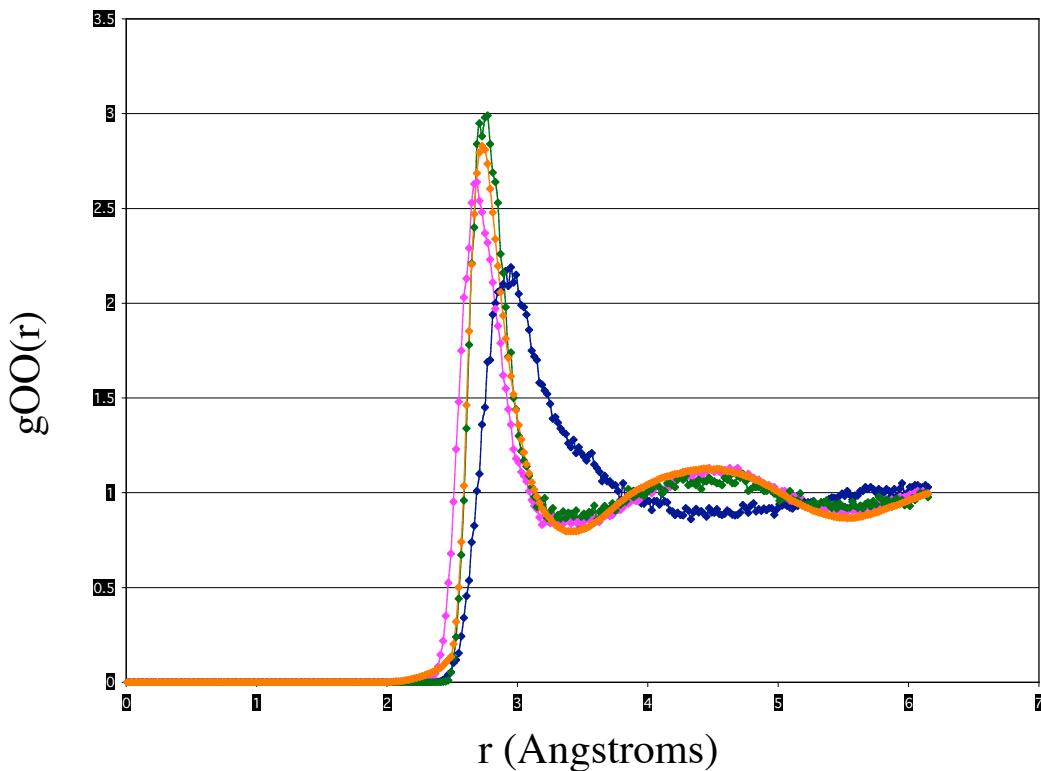
Water hexamer isomers

Binding Energy	DFT B3LYP	EFP1/ DFT	MP2	EFP1/ MP2	CCSD (T)	HF	EFP1/ HF
prism	62.37	61.08	58.25	58.26	55.10	42.86	42.42
cage	61.84	61.53	57.52	57.64	54.30	42.49	41.90
book	61.34	61.79	56.49	56.67	53.10	42.44	41.45
cyclic	60.57	60.65	55.75	55.24	52.20	43.10	41.14
boat	59.13	59.37	54.29	53.92	50.80	42.12	40.09

- basis set: DH(d,p)

-units: kcal/mol

$g_{OO}(r)$: EFP1/HF, EFP1/DFT, SPC/E 62 waters

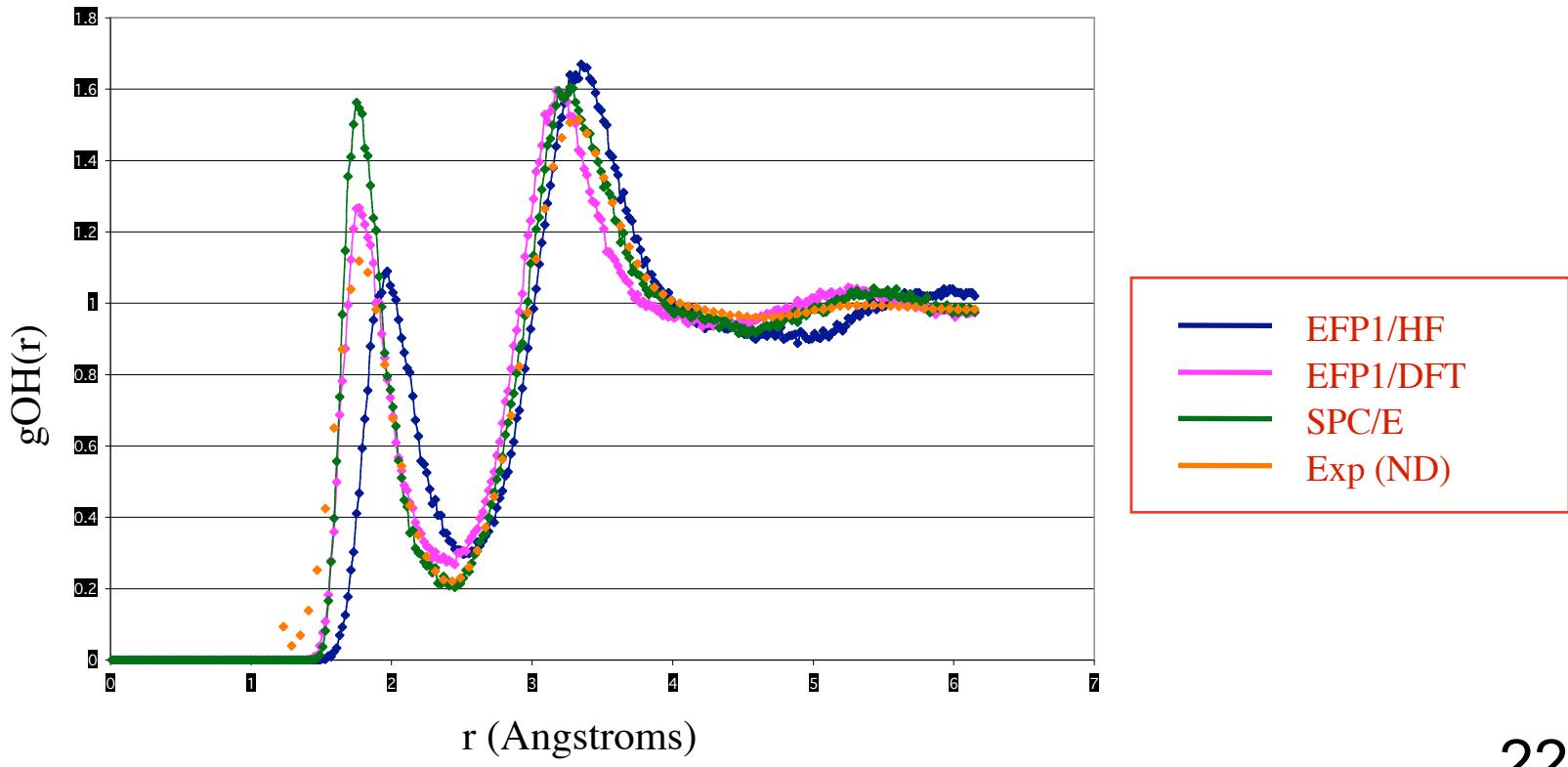


Initial structure: 62 waters,
26 ps equilibration

Timestep size = 1 fs,
Simulation = 5000 fs

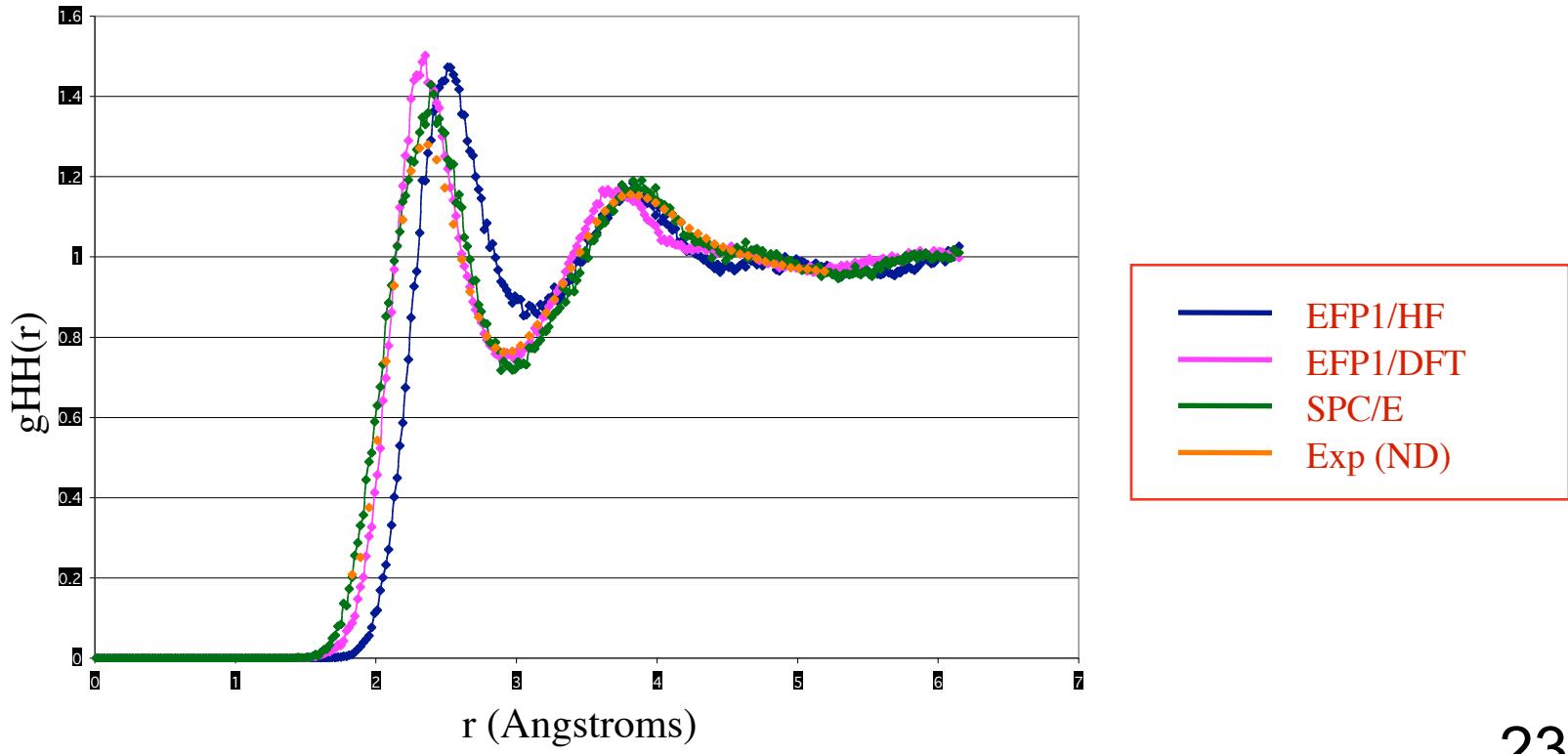
- EFP1/HF
- EFP1/DFT
- SPC/E
- Exp (THG)

$g_{OH}(r)$: EFP1/HF, EFP1/DFT, SPC/E 62 waters



Exp (ND): Neutron Diffraction; Soper et. al.

$g_{\text{HH}}(r)$: EFP1/HF, EFP1/DFT, SPC/E 62 waters



GENERAL EFP METHOD

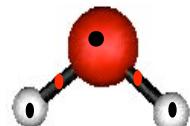
- Jan Jensen
- Mark Freitag
- Ivana Adamovic
- Mol. Phys., 89, 1313 (1996)
- JCP, 108, 4772 (1999)
- JCP, 112, 7300 (2000)

Hartree Fock based EFP

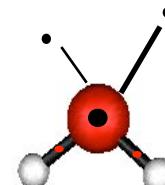
Interaction energy consists of : *electrostatic, polarization and exchange repulsion/charge transfer term*

$$E_{\text{interaction}} = E_{\text{coulomb}} + E_{\text{polarization}} + E_{\text{exchange repulsion/charge transfer}}$$

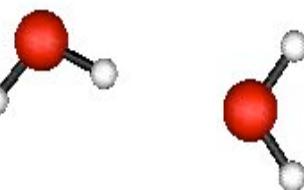
$$E_{\text{interaction}} = \sum_{k=1}^K V_k^{\text{Elec}}(\mu, s) + \sum_{l=1}^L V_l^{\text{Pol}}(\mu, s) + \sum_{m=1}^M V_m^{\text{Re } p}(\mu, s)$$



Distributed
Multipolar expansion



LMO polarizability
expansion

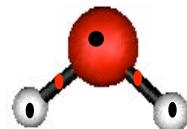


Fit to Functional
Form

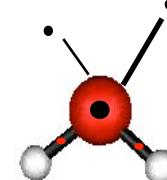
Generalized EFP2 Method

Interaction energy consists of : *electrostatic, polarization and exchange repulsion term*

$$E_{\text{interaction}} = E_{\text{electrostatic}} + E_{\text{polarization}} + E_{\text{exchange repulsion}}$$



Distributed
Multipolar expansion



LMO polarizability
expansion



From first principles
using LMO overlaps

Summary

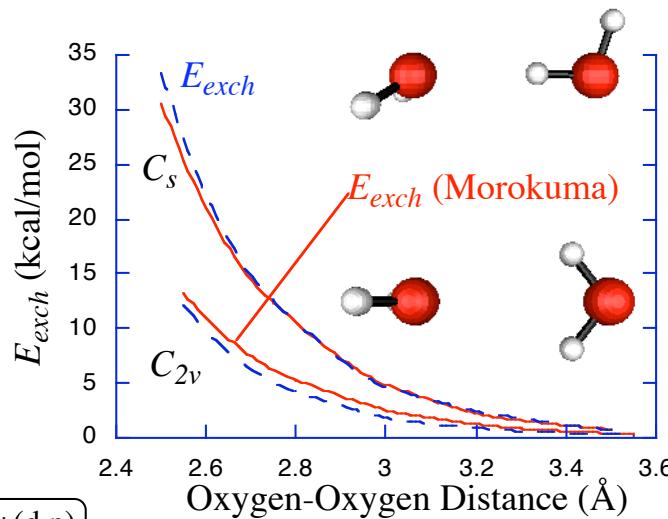
If all approximations presented above are combined, E_{exch} can be approximated as (provided LMOs are used)

$$E_{exch} \approx -2 \sum_{i \in A} \sum_{j \in B} 2 \sqrt{\frac{-2 \ln S_{ij}}{\pi}} \frac{S_{ij}^2}{R_{ij}} - 2 \sum_{i \in A} \sum_{j \in B} S_{ij} \left[\sum_{k \in A} F_k^A S_{kj} + \sum_{l \in B} F_l^B S_{li} - 2T_{ij} \right] \\ + 2 \sum_{i \in A} \sum_{j \in B} S_{ij}^2 \left[\sum_{J \in B} -Z_J R_{il}^{-1} + 2 \sum_{l \in B} R_{il}^{-1} + \sum_{I \in B} -Z_I R_{lj}^{-1} + 2 \sum_{k \in A} R_{kj}^{-1} - R_{ij}^{-1} \right]$$

This equation requires only the computation of intermolecular overlap and electronic kinetic energy integrals, i.e. no two-electron integrals other than those calculated once for the isolated molecules.

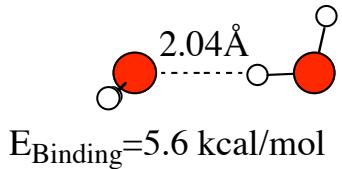
It contains no adjustable parameters, only fixed parameters computed for the isolated molecules, such as the LMOs in some AO basis, Fock matrices in the LMO bases, and the LMO centroids of charge

Numerical Tests



RHF/6-31++(d,p)

EFP(nc)[6-31G(d,p)]



RHF/6-31G(d,p)

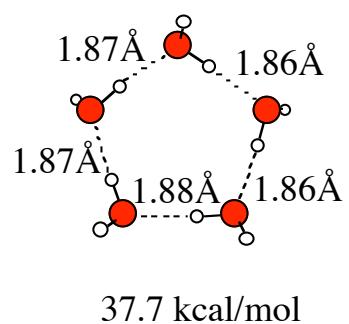
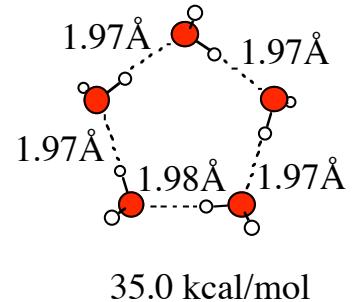
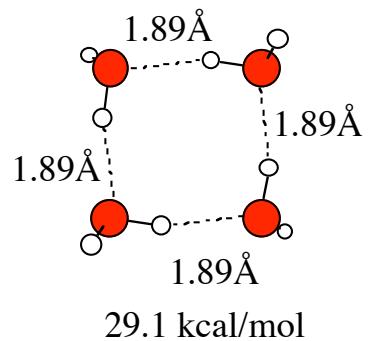
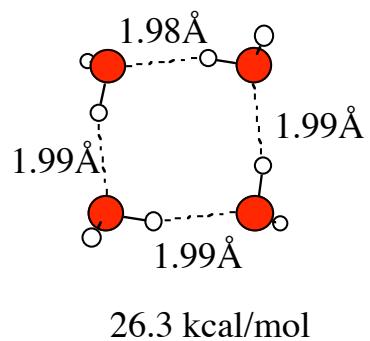
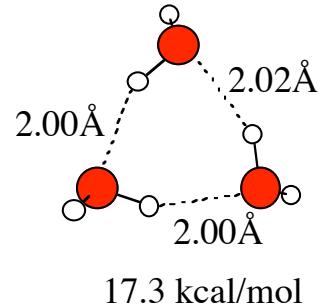
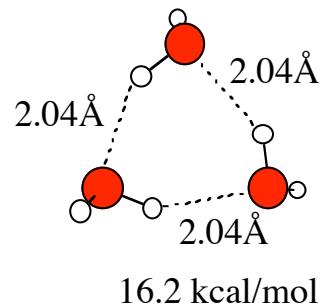
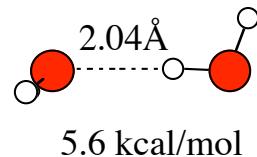


Figure 3. Structures and binding energies of $(\text{H}_2\text{O})_n$, $n=2-5$ at the EFP(nc)[6-31G(d,p)} and RHF/6-31G(d,p) level of theory.

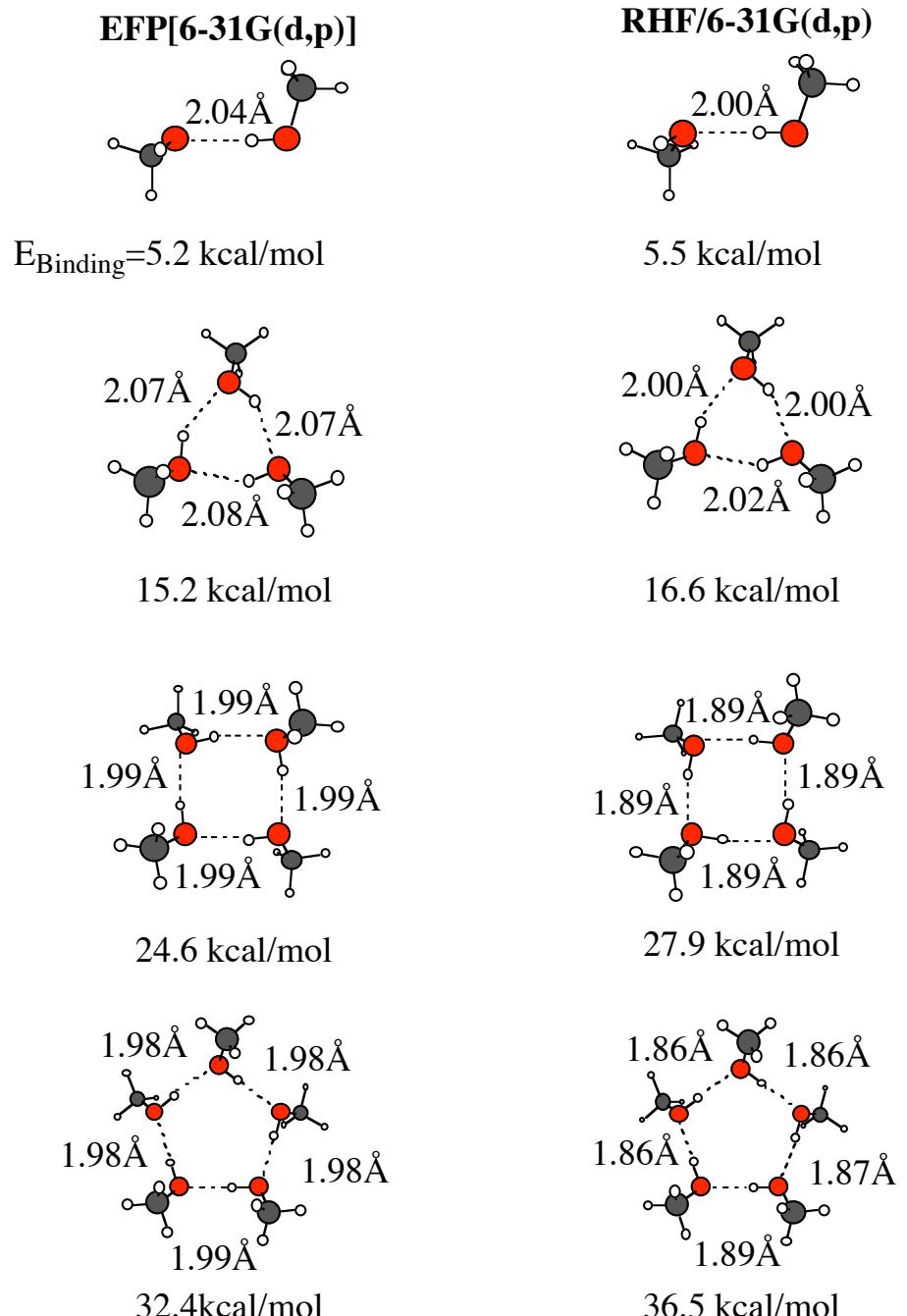


Figure 4. Structures and binding energies of $(\text{MeOH})_n$, $n=2-5$ at the EFP(nc)[6-31G(d,p)] and RHF/6-31G(d,p) level of theory.

EFP Performance: Energy + Gradient Calculation

Method ¹	20 water molecules	62 water molecules	122 water molecules	512 water molecules
<i>Ab initio</i> ²	3.19 hrs	---	---	~157 yrs ³
EFP2	3.3 sec	26.1 sec	95.3 sec	26.8 min
EFP1/HF	0.2 sec	2.6 sec	5.1 sec	97.8 sec
SPC/E ⁴	0.02 sec	0.02 sec	0.1 sec	0.7 sec

¹Run on 1200 MHz Athlon/Linux machine

²*Ab initio*: DZP basis set, ³Assuming N⁴ scaling,

⁴SPC/E = Simple Extended Point Charge model

CONCLUSIONS/FUTURE

- Developments in Progress
 - Analytic *ab initio*/EFP gradient for EFP2
 - Dispersion Term
 - EFP1: Fit to MP2, similar to EFP1/DFT
 - EFP2: From frequency-dependent polarizabilities
 - Generalized Charge Transfer (EFP2)
 - Molecular Dynamics Code (~done)
 - Flexible fragments

CONTINUUM SOLVATION MODELS

- Simplest is Onsager self-consistent reaction field (SCRF) model (\$SCRF)
 - Solute (QM) dipole moment μ polarizes “medium” (solvent) through dielectric ϵ
 - Newly polarized solvent alters solute dipole moment
 - Iterated to self-consistency
 - Accomplished by adding new term to QM Hamiltonian

ONSAGER SCRF MODEL

- $V_\sigma = -r \cdot R$
 - r = position vector
 - R is proportional to molecular dipole moment
 - $R = g\mu$
 - μ = dipole vector
 - $g = 2(\epsilon-1)/[(2\epsilon+1)(a^3)]$
 - a = radius of cavity
 - Usually assume spherical cavity
 - Radius can be pretty arbitrary
 - Adds simple $\langle \chi_i | x | \chi_j \rangle$ integrals - very cheap

PCM MODEL

- Polarizable Continuum Model (PCM)
 - Tomasi et al., Chem. Phys. Lett., 255, 327 (1996)
 - Van der Waals type surface cavity
 - Uses detailed knowledge of electrostatic potential
 - Cavity dispersion potential determined from surface area
 - Can include dispersion effects
 - Interfaced with EFP in GAMESS: \$PCM
 - See both input and reference sections in manual

APPLICATIONS

- Water Clusters (JCP, JPC)
- Formamide Internal Rotation (JCP)
- Formamide UV Shifts (JCP)
- Glycine Neutral <-> Zwitterion (JPC, JCP)
- Chemical Reactions (JPC)
- Solvation of Electrolytes (JPC), ions
- Solvation of Alcohols (JACS)
- Catalyzed Hydroformylation Rxn (Organomet)

MENSHUTKIN REACTION: SIMON WEBB

- N. Menshutkin, *Z. Phys. Chem.*, **1890**, 5, 589; 6, 41
 - $\text{R}_3\text{N} + \text{RX} \rightarrow \text{R}_4\text{N}^+\text{X}^-$
- **Reaction rate increases with polarity of solvent**
- **How does EFP method do?**

PREVIOUS CALCS

- M. Sola etal
 - NH₃ + CH₃Br
 - Two *ab initio* RHF/3-21G waters
 - Continuum model for solvent
 - Free energy of activation = 8.3 kcal/mol
- J. Gao etal
 - QM/MM (AM1/TIP3P) study of NH₃ + CH₃Cl
 - Free energy of activation = 26.3
- J. Rivail etal
 - Continuum study of NH₃ + CH₃Cl
 - Free Energy of activation ≈ 23 kcal/mol

EXPERIMENTAL RESULTS

- K. Okamoto et al.
 - $\text{NH}_3 + \text{CH}_3\text{I}$
 - Free energy of activation = 23.5 kcal/mol
- Nothing known for $\text{NH}_3 + \text{CH}_3\text{Br}$

COMPUTATIONAL METHODS

- NH₃ + CH₃Br (GAMESS)
- Solute treated with *ab initio* methods
- Solvent treated with both *ab initio* & EFP
- Geometries: RHF or MP2
- Basis set: VDZP + diffuse sp on Br

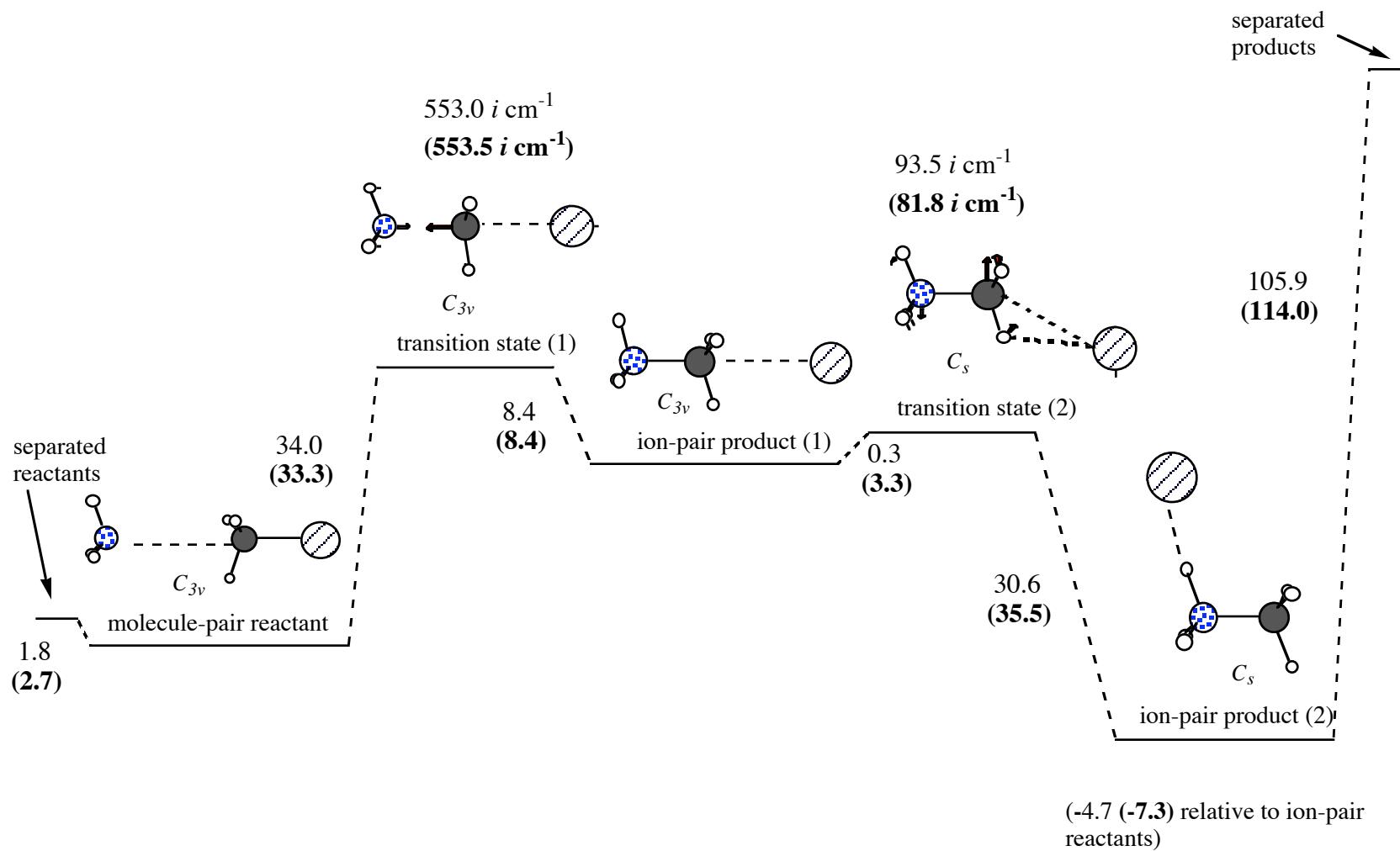
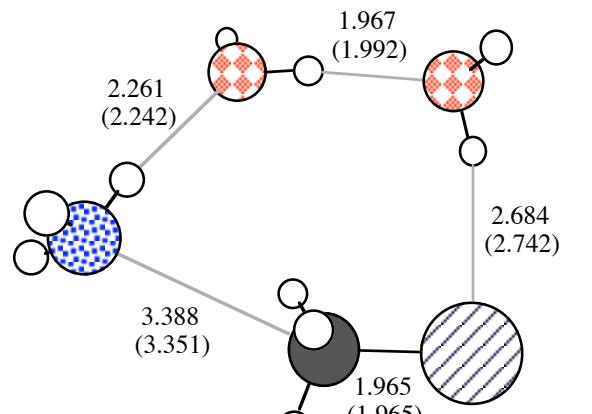


Figure 2. The RHF/DZVP and MP2/DZVP potential energy surfaces of the Menshutkin reaction (R3) in the gas phase at 0 K (no ZPE corrections). Energies are in kcal/mol. Harmonic vibrational frequencies and displacements (see arrows) are shown for transition states. Diagram is not to scale. MP2/DZVP values are in bold type.

() = fragment



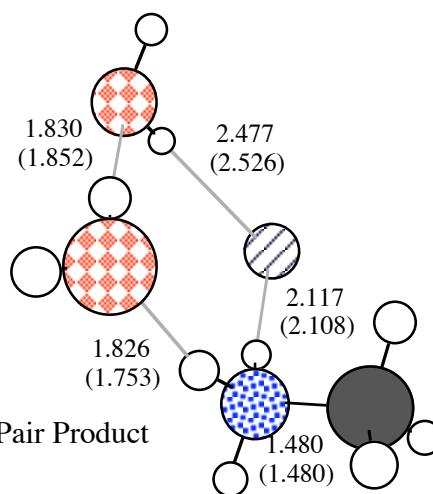
Molecule-Pair Reactant

Mulliken charges

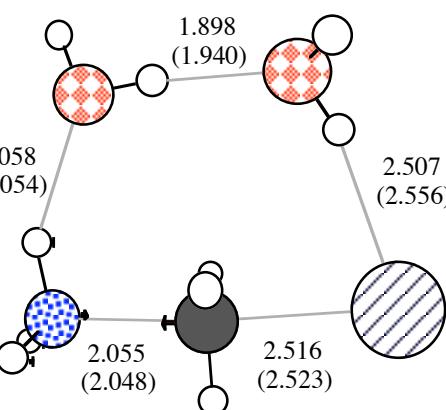
N -.783 (-.815)
3H .783 (.823)

C -.251 (-.240)
3H .509 (.502)

Br -.262 (-.271)



Ion-Pair Product



Transition State $536.5 i \text{ cm}^{-1}$
 $(538.0 i \text{ cm}^{-1})$

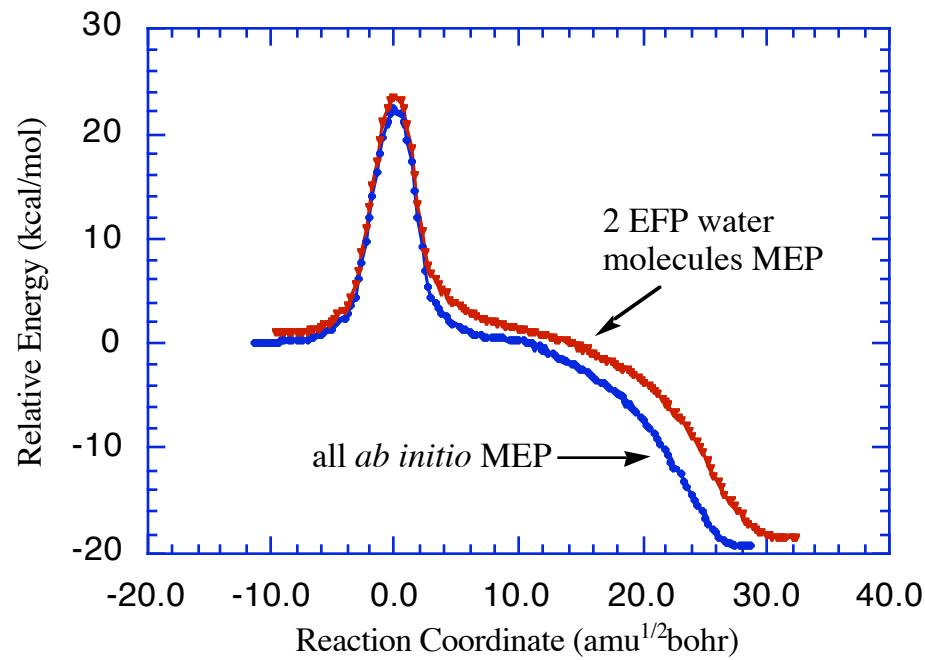
Mulliken charges

N -.440 (-.504)
3H 1.015 (1.117)

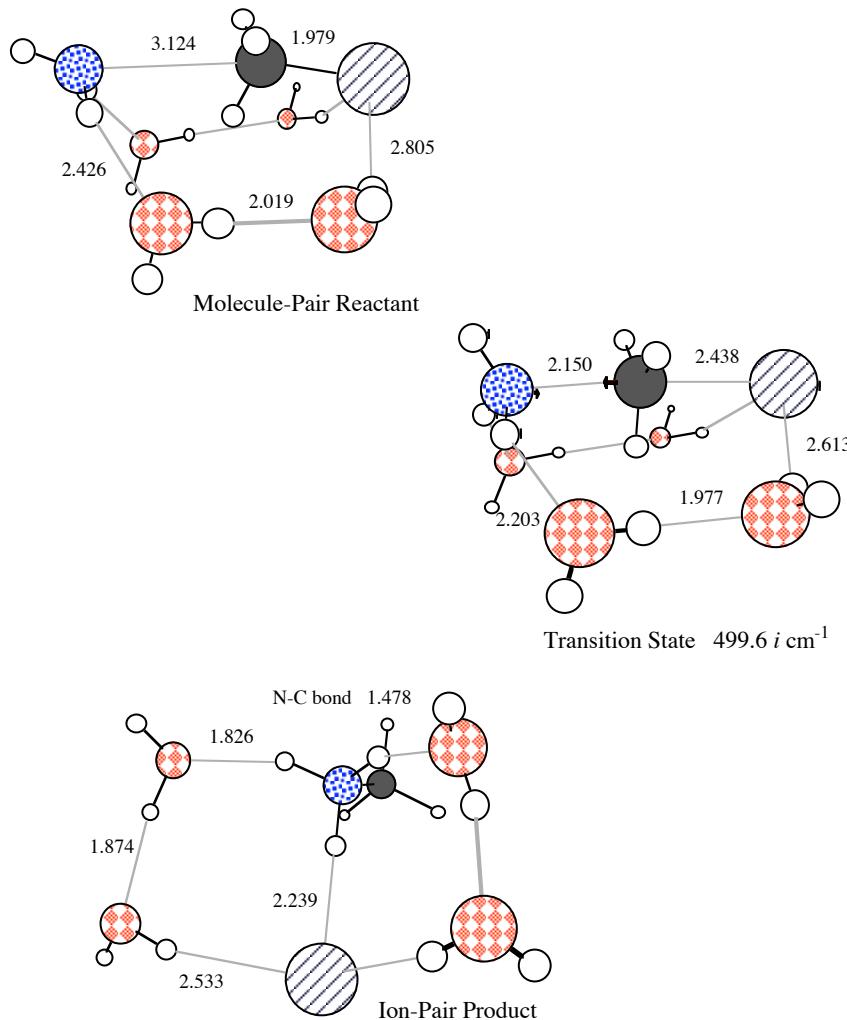
C -.253 (-.247)
3H .491 (.487)

Br -.818 (-.853)

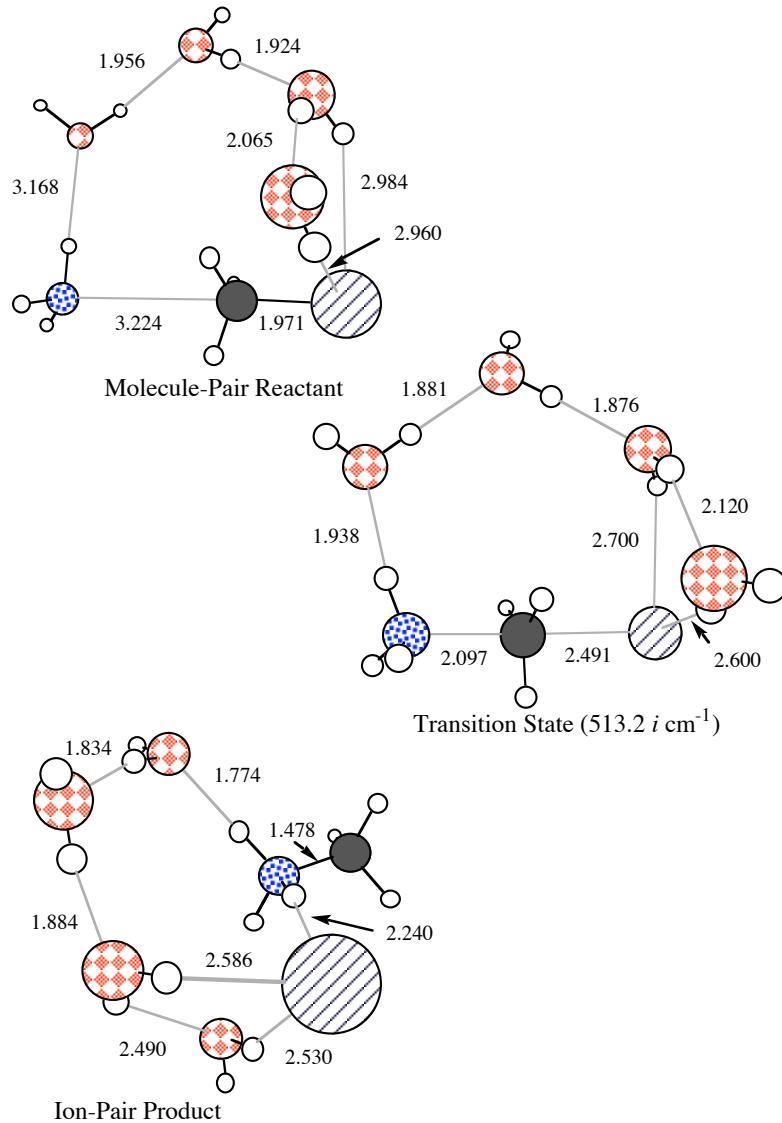
MEP FOR 2 WATERS

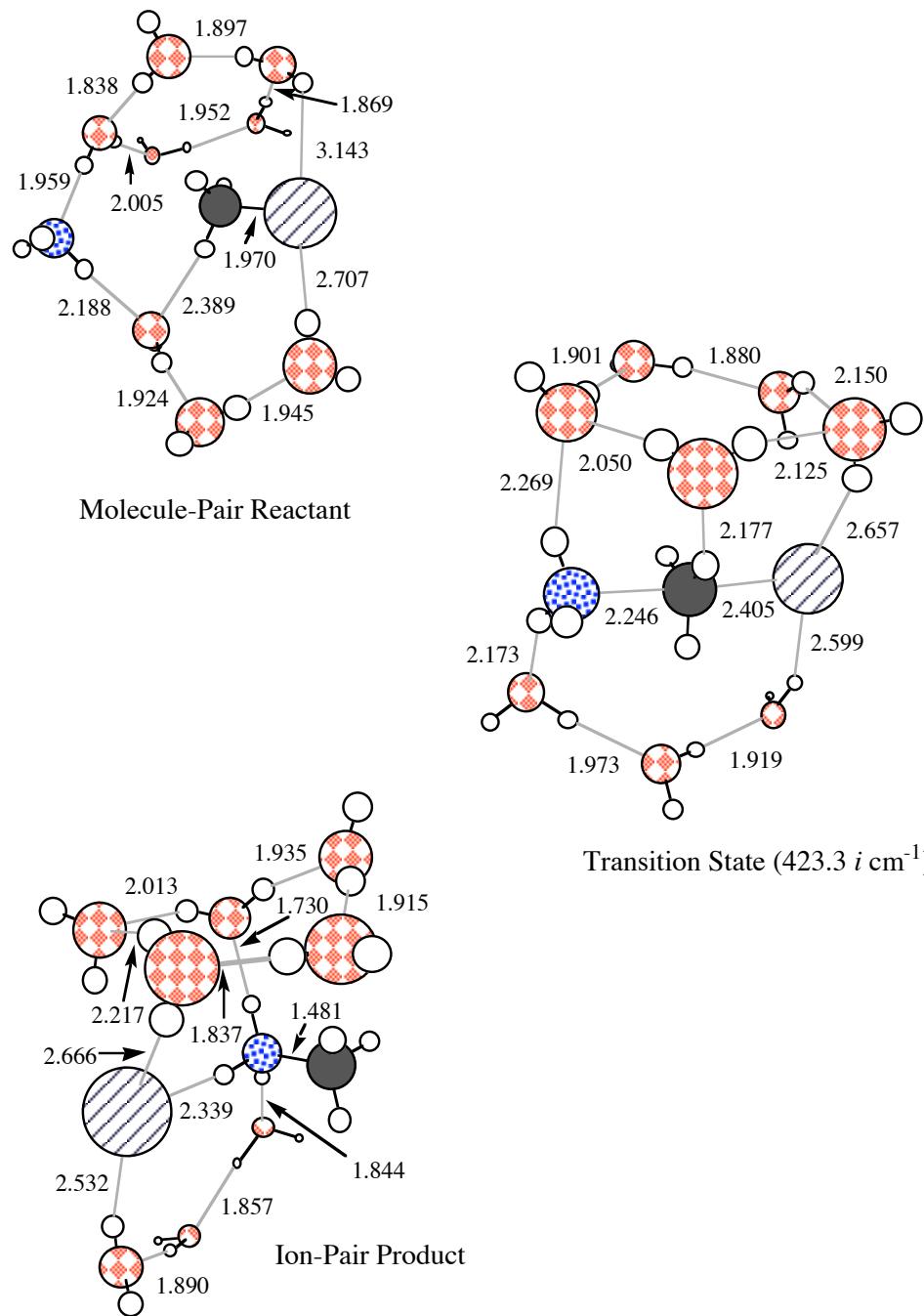


4 WATERS (A)



4 WATERS (B)





# waters	ΔE (kcal/mol)		
		EFP	AI
0	I-P REAC		0.0
	TS		34.0
	I-P PROD		-4.7
2	I-P REAC	0.0	0.0
	TS	22.5	22.2
	I-P PROD	-19.4	-19.2
4	A	I-P REAC	3.9
		TS	17.6
		I-P PROD	-30.7
4	B	I-P REAC	0.0
		TS	18.0
		I-P PROD	-26.2
6	A	I-P REAC	0.9
		TS	23.0
		I-P PROD	-19.6
6	B	I-P REAC	0.0
		TS	16.0
		I-P PROD	-29.1
8		I-P REAC	0.0
		TS	20.3
		I-P PROD	-31.4
			-31.3

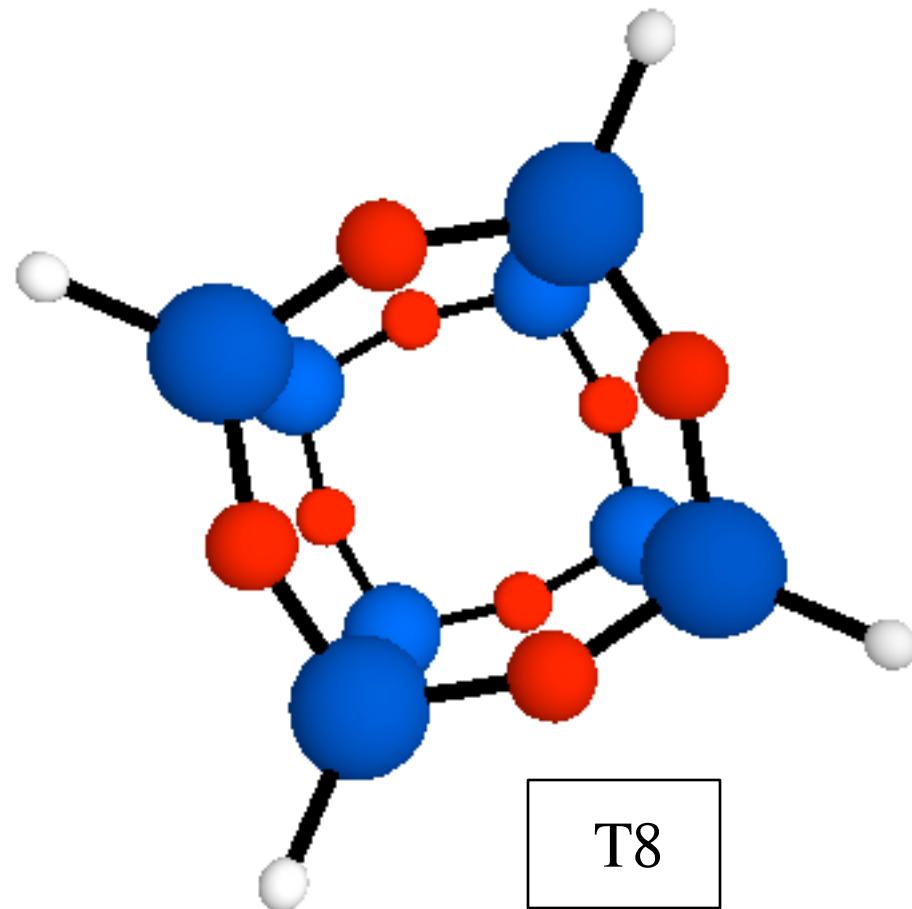
# waters	ΔG_{298} (kcal/mol)	
	EFP	AI
0	I-P REAC	0.0
	TS	40.6
	I-P PROD	2.8
2	I-P REAC	0.0
	TS	28.3
	I-P PROD	-10.2
8	I-P REAC	0.0
	TS	22.7
	I-P PROD	-23.8

TIMINGS

# Waters	Wall Clock				Δ (Wall Clock)	
	0	8	8	9	AI	EFP
2		4006	1376		3117	487
		(5399)	(2118)		(3672)	(391)
4		11768	1658		7762	282
		(17905)	(2422)		(12506)	(304)
6		-	2054		-	396
		(26684)	(2981)		(8779)	(559)
8		-	1752		-	221
		(45029)	(3134)		(18345)	(153)

() = Direct

POSS COMPOUNDS: TAKAKO KUDO

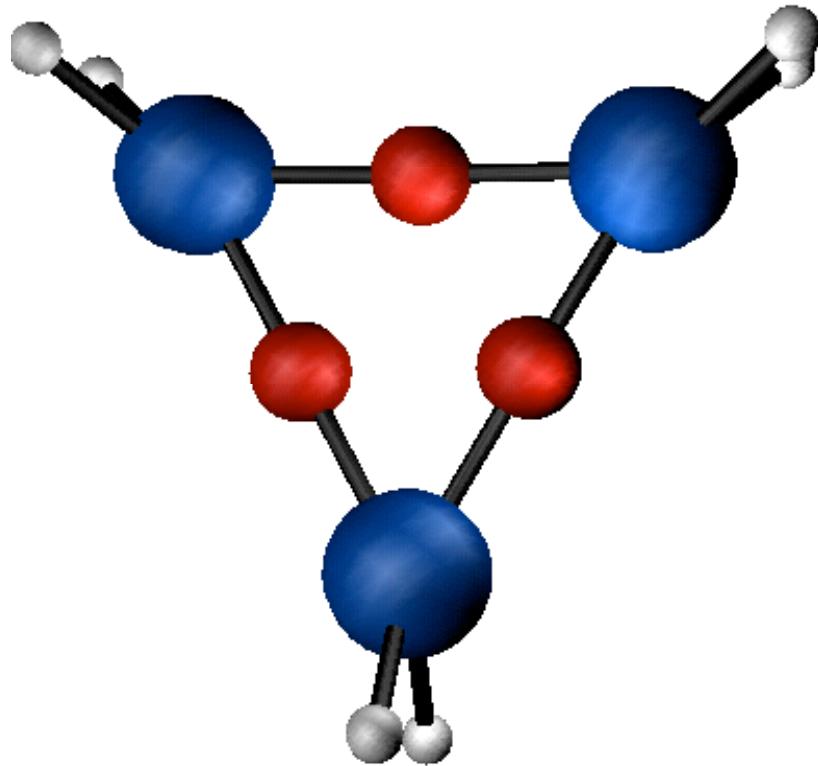


T8

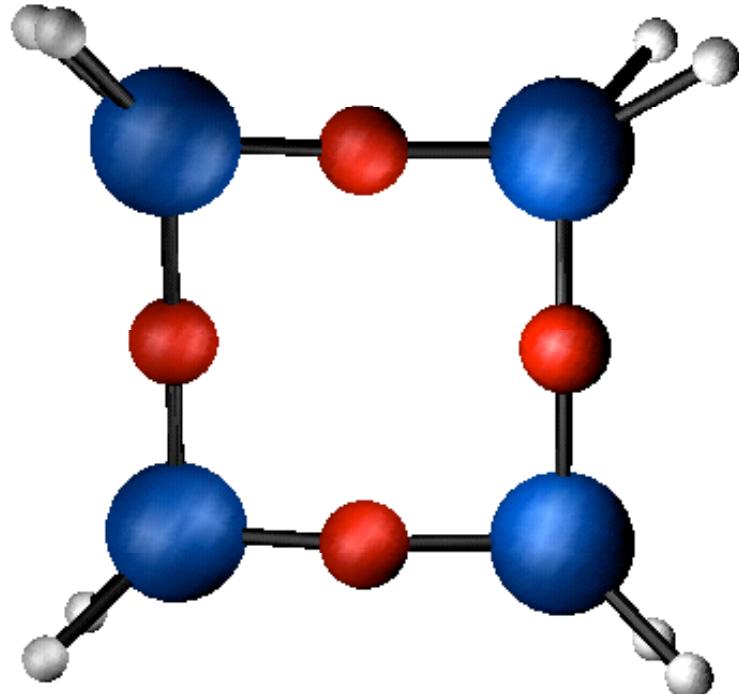
POSS COMPOUNDS

- Polyhedral Oligomeric Silsesquioxanes
- Resistant to Extreme Environments
- Coatings, Viscosity Modifiers, Pre-ceramics
- Formation Mechanism Unknown
- Synthesis of Alternative Structures Desirable
- Synthesis of Incompletely Condensed Species Desirable

2-D RINGS

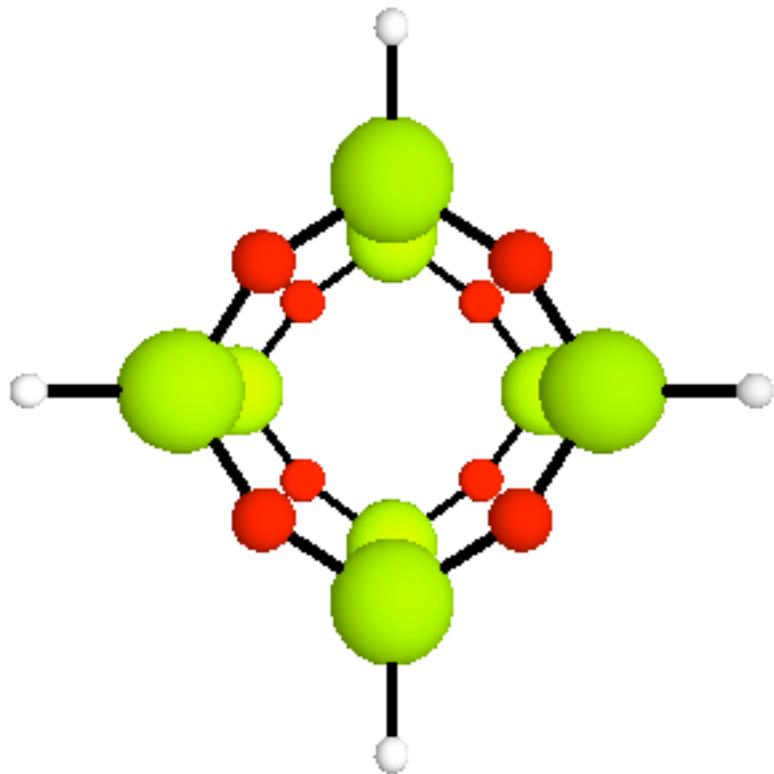


D3

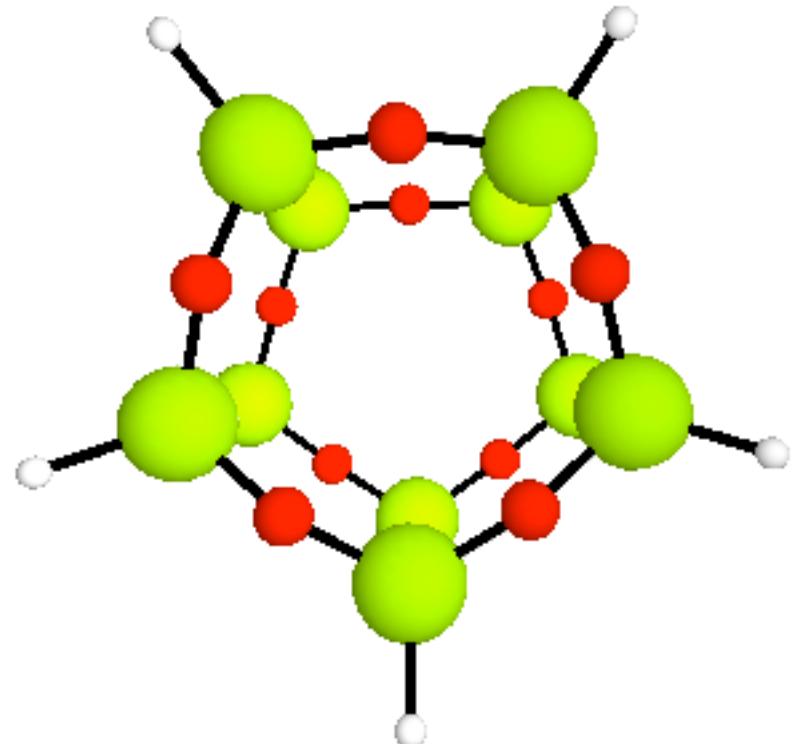


D4

3-D CAGES



T8



T10

MECHANISM FOR FORMATION

- Hydrolysis of RSiX_3 ($\text{R} = \text{H}, \text{Cl}, \text{OMe}$)
- Condensation of RSi(OH)_3 to disiloxanes
- Condensation of disiloxanes to D_3, D_4
- Condensation of D_3, D_4 to POSS
- Issues:
 - **Role of solvent**
 - Substituent effects

COMPUTATIONAL METHODS

- Geometries
 - RHF, MP2, B3LYP
- Basis Sets
 - 6-31G(d), 6-311G(d), Extended
- Energies
 - MP2, CCSD(T)
- GAMESS

Relative energies (kcal/mol) for the stepwise hydrolysis of HSiCl₃

level	R ^b	CM1 ^a	TS ^{a,b}	CM2 ^a	P ^a
1. HSiCl₃ + H₂O → HSiCl₂OH + HCl					
RHF/6-31G*	0.0	-4.0	30.0 (13.1)	-9.0	-6.2
MP2/6-31G*	0.0	-5.9	23.0 (-1.2)	-9.9	-5.3
2. HSiCl₂OH + H₂O → HSiCl(OH)₂ + HCl					
RHF/6-31G*	0.0	-3.4	20.3 (4.9)	-8.1	-3.2
MP2/6-31G*	0.0	-5.3	14.7 (-6.1)	-9.8	-2.9
3. HSiCl(OH)₂ + H₂O → HSi(OH)₃ + HCl					
RHF/6-31G*	0.0	-5.2	17.0 (4.5)	-8.3	-3.6
MP2/6-31G*	0.0	-7.0	12.3 (-7.4)	-9.8	-2.7

a) R=reactant, CM1=complex 1, TS=transition state, CM2=complex 2,
P=products

b) Values in parentheses correspond to the presence of an additional water molecule.

CONDENSATION OF SILANOL

- $\text{H}_3\text{SiOH} + \text{H}_3\text{SiOH} \rightarrow \text{H}_3\text{SiOSiH}_3$
- $\text{HSi(OH)}_3 + \text{HSi(OH)}_3 \rightarrow \text{H(OH)}_2\text{SiOSi(OH)}_2\text{H}$

Relative energies (kcal/mol) for the condensation of H₃SiOH and HSi(OH)₃

Method	Reactants	Intermediate	TS	Product
1. H₃SiOH x 2 → H₃SiOSiH₃ + H₂O				
RHF/6-31G*	0.0	-5.9 (-13.9)	35.8 (23.5)	-5.6
MP2/6-31G*	0.0	-8.2 (-19.8)	20.5 (0.4)	-4.7
CCSD(T)/6-31G* ^{a)}	0.0	-8.0 (-19.1)	22.4 (3.9)	-4.9
2. HSi(OH)₃ x 2 → H(OH)₂SiOSi(OH)₂H + H₂O				
RHF/6-31G*	0.0	-10.4 (-23.1)	30.4 (16.7)	-7.2
MP2/6-31G*	0.0	-16.9 (-34.6)	10.9 (-9.3)	-9.9
CCSD(T)/6-31G* ^{a)}	0.0	-16.5 (-33.6)	12.8 (-6.6)	-10.1

3. Single point energies at MP2/6-31G* geometries.

4. Values in parentheses correspond to the presence of an additional water.

Effect of Waters on First Hydrolysis Step



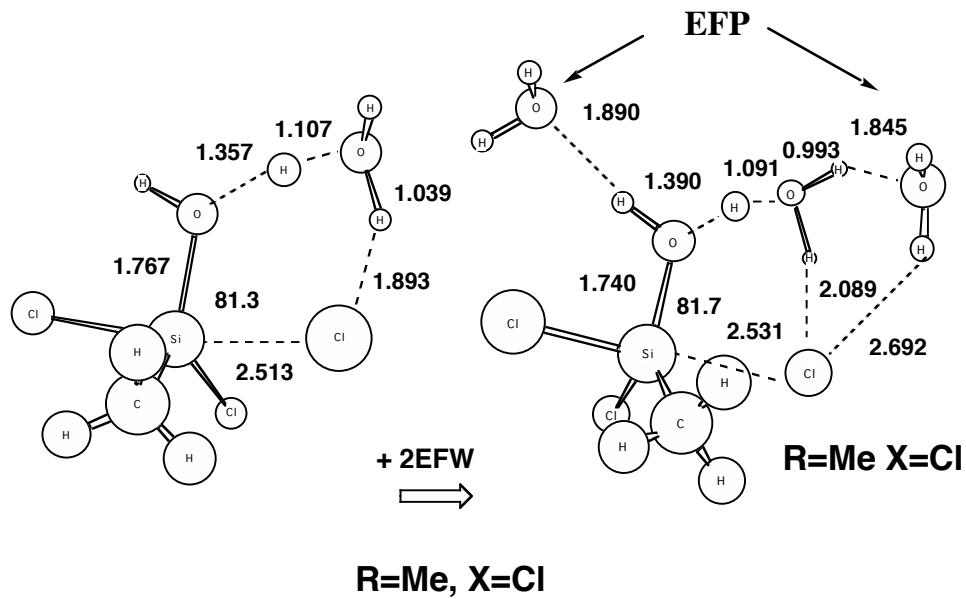
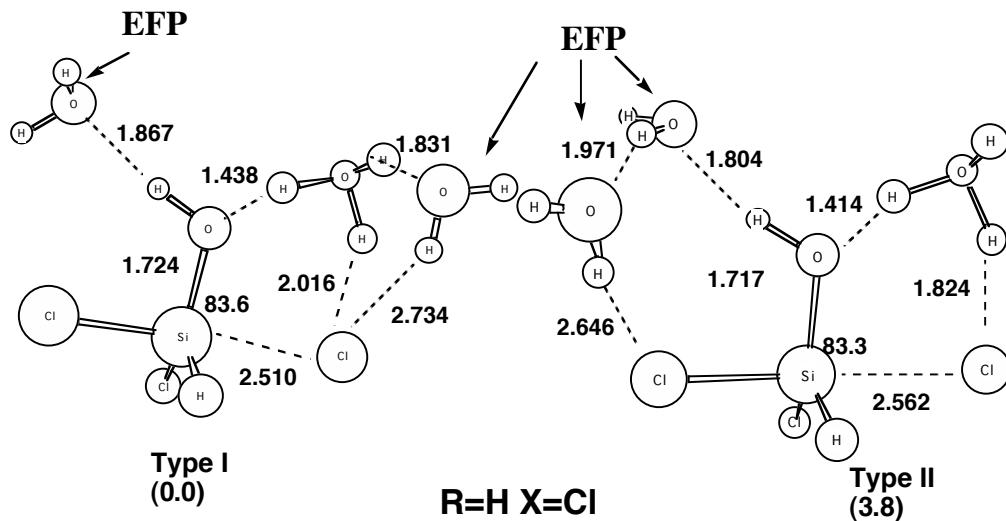
MP2/6-31G*

R	X	Energy barrier (kcal/mol)
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	direct	+ H ₂ O	+ 2EFW
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H	Cl	23.0	-1.2	-14.4
Me	Cl	23.6	1.7	-10.5

**Effect of waters on RSiX_3 hydrolysis,
Step 1: MP2/6-31G(d)**

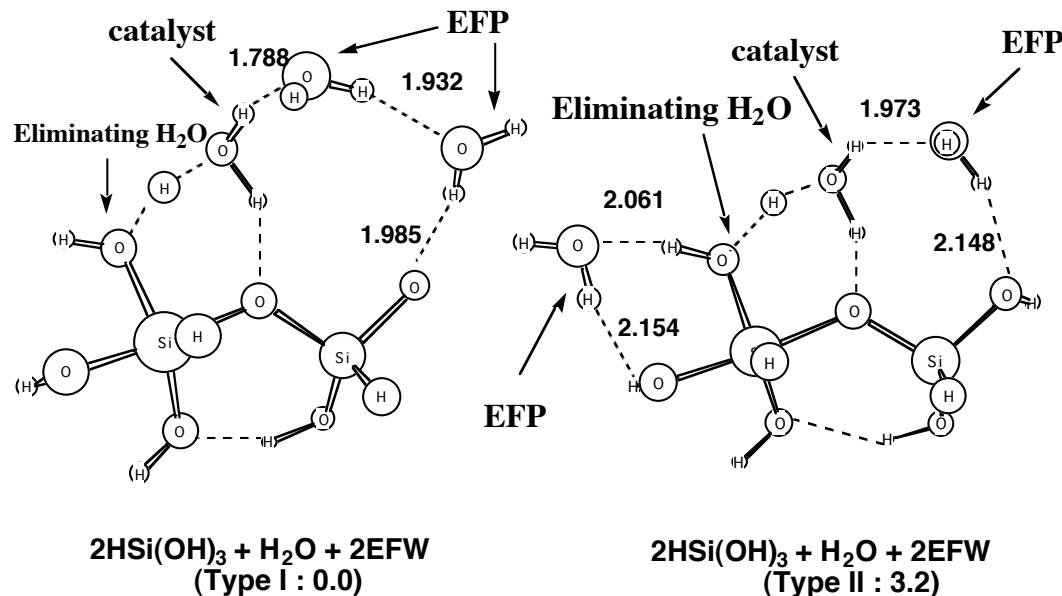
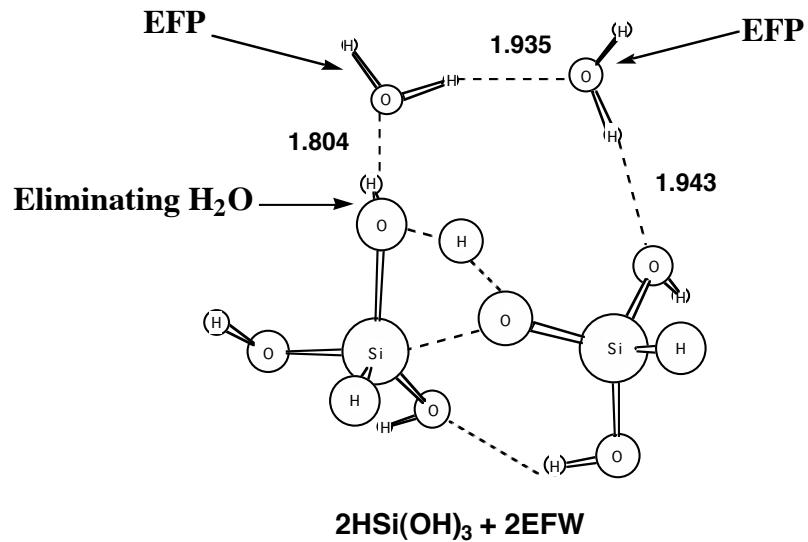


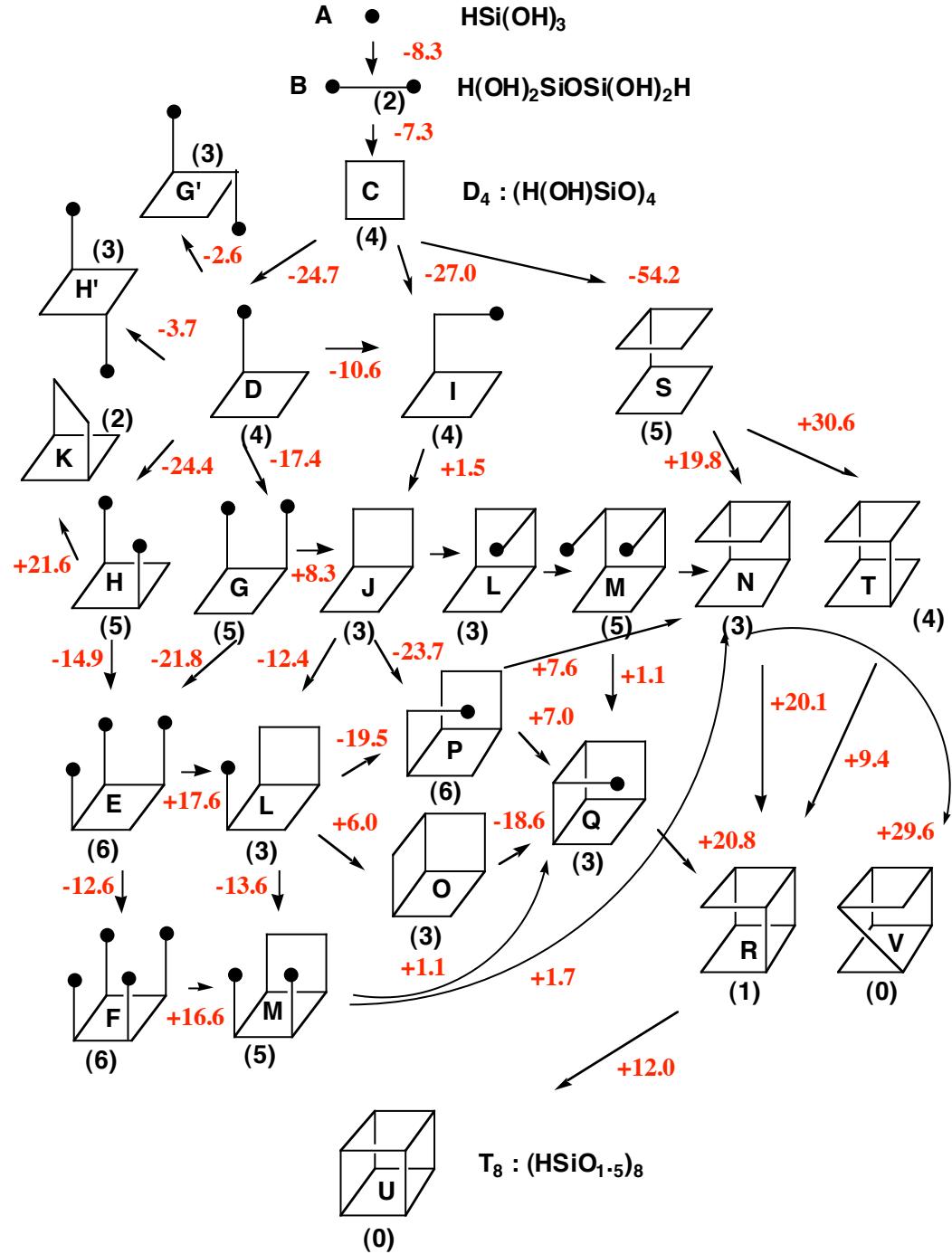
Effect of Waters on HSi(OH)₃ Condensation

	kcal/mol	
	HF/6-31G*	MP2/6-31G*
Direct	30.4	10.9
+ H ₂ O	16.7	-9.3
+ 2EFW	22.8	4.2
+ H ₂ O + 2EFW		
Type I	5.4	-18.8
Type II	8.6	-15.6

Condensation of HSi(OH)_3 with Effective Fragment Waters

Transition Structures: MP2/6-31G(d)





scheme 2

CONCLUSIONS

- Correlation is Essential for Quantitative Results
- MP2 Appears to be Sufficient
- B3LYP is Reliable for Geometries
- Additional Water Reduces Barrier to Nearly Zero for Each Step
- Large Solvation Effects: Other solvents?
- Substituent Effects Relatively Small
- Dynamics?

CONCLUSIONS/FUTURE

- EFP is a Viable Method for Solvation
- Developments in Progress
 - Analytic *ab initio*/EFP gradient for EFP2
 - Dispersion Term
 - EFP1: Fit to MP2, similar to EFP1/DFT
 - EFP2: From frequency-dependent polarizabilities
 - Generalized Charge Transfer (EFP2)
 - Molecular Dynamics Code (~done)
 - Flexible fragments